For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

1. (**Amended**) A method for inhibiting reduction of bone density in a mammalian patient having a pathological condition in which bone density is decreased, comprising inhibiting in the patient the formation of a tertiary complex of Interleukin-11 (IL-11), Interleukin-11 receptor (IL-11R), and glycoprotein 130 (gp130).

2. (**Amended**) The method of claim 1, which comprises administering to the patient an effective amount of a substance which inhibits, *in vivo*, the formation of a tertiary complex of IL-11, IL-11R, and gp130.

3. (**Amended**) The method of claim 2, wherein the pathological condition is postmenopausal bone loss.

4. (**Amended**) The method of claim 2, wherein the substance is a mutant IL-11R.

5. (**Amended**) The method of claim 4, wherein the substance is a mutant IL-11R with at least one mutation in its gp130 binding region.

6. (**Amended**) The method of claim 5, wherein the substance is a mutant IL-11R having at least one of the following mutations: D282→G282, A283→D283, G286→D286, H289→Y289, and V291→L291.

7. (**Amended**) The method of claim 6, wherein the substance is a mutant IL-11R having the mutation H289→Y289.

8. (**Amended**) The method of claim 6, wherein the substance is a soluble mutant IL-11R.

9. (**Amended**) The method of claim 8, wherein the mutant IL-11R is a human IL-11R.

10. (**Amended**) The method of claim 2, wherein the substance is an anti IL-11 antibody.

11. (**Amended**) The method of claim 2, wherein the substance is an IL-11 binding peptide.

12. (**Amended**) The method of claim 11, wherein the substance is an IL-11 binding peptide having an amino acid sequence which specifically binds IL-11 in the region normally bound by IL-11R.

13. (**Amended**) The method of claim 12, wherein the substance is a peptide comprising the sequence identified by SEQ ID No. 5.

14. (**Amended**) The method of claim 2, wherein the substance is a small molecule no more than 30 kd in molecular weight.

15. (**Amended**) The method of claim 2, wherein the substance is an IL-11 antagonist.

16. (**Amended**) The method of claim 2, wherein the substance is an IL-11R binding peptide.

17. (**Amended**) The method of claim 2, wherein the substance is an anti IL-11R antibody which inhibits interactions between IL-11 and the IL-11R.

18. (**Amended**) The method of claim 2, wherein the substance is an anti IL-11R antibody which inhibits interactions between IL-11R and gp130.

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40. (**Amended**) A composition useful in inhibiting IL-11 / IL-11R bindings comprising an antibody which specifically binds the IL-11R and blocks bindings between IL-11 and IL-11R.

41. (**Amended**) A composition useful in inhibiting IL-11R / gp130 bindings via the gp130 binding site on IL-11R comprising an antibody which specifically binds the IL-11R and blocks bindings between gp130 and IL-11R.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (**Amended**) A method for inhibiting reduction of bone density in a mammalian patient having [process of treating or alleviating the symptoms of] a pathological condition in which bone density is decreased, comprising [which comprises] inhibiting[,]in[a mammalian] the patient [suffering from such a condition,] the formation of a tertiary complex of Interleukin-11 (IL-11), Interleukin-11 receptor (IL-11R), and glycoprotein 130 (gp130).

2. (**Amended**) The method [process] of claim 1, which comprises administering to the patient an effective amount of a substance which inhibits, *in vivo*, the formation of a tertiary complex of IL-11, IL-11R, and gp130.

3. (**Amended**) The method [process] of claim 2, wherein the pathological condition is postmenopausal bone loss.

4. (**Amended**) The method [process] of claim 2, wherein the substance is a mutant IL-11R.

5. (**Amended**) The method [process] of claim 4, wherein the substance is a mutant IL-11R with at least one mutation in its gp130 binding region.

6. (**Amended**) The method [process] of claim 5, wherein the substance is a mutant IL-11R having at least one of the following mutations: D282→G282, A283→D283, G286→D286, H289→Y289, and V291→L291.

7. (**Amended**) The method [process] of claim 6, wherein the substance is a mutant IL-11R having the mutation H289→Y289.

8. (**Amended**) The method [process] of claim 6, wherein the substance is a soluble mutant IL-11R.

9. (**Amended**) The method [process] of claim 8, wherein the mutant IL-11R is a human IL-11R.

10. (**Amended**) The method [process] of claim 2, wherein the substance is an anti IL-11 antibody.

11. (**Amended**) The method [process] of claim 2, wherein the substance is an IL-11 binding peptide.

12. (**Amended**) The method [process] of claim 11, wherein the substance is an IL-11 binding peptide having an amino acid sequence which specifically binds IL-11 in the region normally bound by IL-11R.

13. (**Amended**) The method [process] of claim 12, wherein the substance is a peptide comprising the sequence [Arg Arg Leu Arg Ala Ser Trp]identified by SEQ ID No. 5.

14. (**Amended**) The method [process] of claim 2, wherein the substance is a small molecule no more than 30 kd in molecular weight.

15. (**Amended**) The method [process] of claim 2, wherein the substance is an IL-11 antagonist.

16. (**Amended**) The method [process] of claim 2, wherein the substance is an IL-11R binding peptide.

17. (**Amended**) The method [process] of claim 2, wherein the substance is an anti IL-11R antibody which inhibits interactions between IL-11 and the IL-11R.

18. (**Amended**) The method [process] of claim 2, wherein the substance is an anti IL-11R antibody which inhibits interactions between IL-11R and gp130.

40. (**Amended**) A composition [of matter] useful in inhibiting IL-11 / IL-11R [interactions]bindings comprising an antibody which specifically binds the IL-11R and blocks [interactions]bindings between IL-11 and IL-11R.

For amendments in the claims:

Applicants have amended claim 13 to comply with the requirement of using SEQ ID No. for amino acid sequences longer than four amino acids.

Claim rejections under 35 USC §112, first paragraph

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph because "the specification does not enable any person skilled in the art ... to practice the invention commensurate with the scope with these claims."

Particularly, the Examiner alleges that claim 1 is overly broad since "[t]he claim language encompasses situations not described in the specification that m[a]y result in 'pathological conditions with as resulting decrease in bone density' other than postmenopausal bone loss." Applicants submit that in page 2, first paragraph, the instant specification states that increased bone resorption is the hallmark of at least several pathological conditions (e.g., metastatic bone cancer, myeloma, and Paget's disease) in addition to postmenopausal bone loss. Page 1 of the specification also teaches that bone remodeling is a balance between bone formation by osteoblasts and bone resorption by osteoclasts. Therefore, loss of bone density and bone mass (osteoporosis) as a result of pathological conditions such as those listed above necessarily involves the same general mechanism of affecting at least one of the two processes (formation and resorption). It follows that a treatment that successfully inhibits bone loss in one disease would be expected to inhibit bone loss in a different disease. For example, Chapurlet and Meunier (Rev Chir Orthop Reparatrice Appar Mot, 1998, 84(8):743-51, French, see English abstract attached as **Exhibit A**) show that Paget's disease of bone, bone fibrous dysplasia, and osteoporosis are all characterized by abnormal bone remodeling, and that bisphosphonates (one of the most commonly used drug for osteoporosis treatment) are effective in treating all three conditions.

It may be true, as the Examiner suggests, that each of the symptoms of a particular multi-symptom disease may have to be treated with a different approach, but no single drug is expected to alleviate all symptoms of the disease in question. Nevertheless, although desired and non-exclusive, the pending claims do not require that the method alleviate all symptoms of a condition,

but merely the bone density / mass loss symptom of the condition. Accordingly, this ground of rejection fails to take into account the specific features recited in the pending claims, which are narrowly tailored to the treatment of reduction in bone density.

In view of the above arguments, the specification is enabling to the full scope of the claims. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action also states that claim 2 is overly broad and questions the nature of the recited "substance" and how to practice the invention covered by claim 2. Specifically, the Office Action asserts that "the mechanism of action of these different agents is not necessarily identical and inhibition of ternary complex formation *in vivo* in the presence or absence of 'a substance' as claimed is not predictable." Applicants respectfully disagree. As the Examiner admits, the specification has set forth "several reagents, including antibodies, binding peptides directed against IL-11, or IL-11R or gp130 in addition to several unnamed small molecules..." Also in page 7, lines 9-19, the specification sets forth exemplary "substances" of widely varying classes that perform this function and would be expected to be useful in the presently claimed methods. Accordingly, Applicants submit that the metes and bounds of the term "substance" would be clear to one of skill in the art, and one of ordinary skill in the art would reasonably expect that substances having the recited function would be useful in the claimed methods.

As to the Examiner's asserted "unpredictability" of *in vivo* treatment using those substances, Applicants submit that the Office Action has set forth neither specific evidence nor scientific reasoning to support these assertions. Pursuant to MPEP 2164.04, "in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention... As stated by the court, 'it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.' 439 F.2d at 224, 169 USPQ at 370." (emphasis original). The Office Action only mentions that "the mechanism of action of these different agents is not necessarily identical," but does not specify why this is so or provide any reasonable basis for

concluding that any significant difference in fact exists. Moreover, the Office Action fails to explain why, even if true, such differing mechanisms would lead to unpredictability of the claimed *in vivo* treatment method, demonstrated to be successful using one of the disclosed agents. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action also asserts that "recitation of 'mutant IL-11R' in claim 4 is overly broad because it is not possible to test all possible mutations through out the entire sequence of IL-11R or even in the region of IL-11R sequence that can bind to IL-11." Applicants submit that claim 4 is directed to a method of inhibiting the ternary complex formation *in vivo* by administering to the patient an effective amount of a mutant IL-11R. Since "one does not look to the claims but to the specification to find out how to practice the claimed invention" (MPEP 2164.08), Applicants submit that there is no need to test *all* possible mutations throughout the entire sequence of IL-11R to identify such a mutant IL-11R.

Secondly, the specification teaches the necessary steps involved in generating further soluble IL-11R mutants, as shown in page 9, first full paragraph and Figure 1B. Applicants submit that the mentioned techniques such as PCR, subcloning, site-directed mutagenesis and screening for binding mutants are all standard molecular biology procedures, and such experiments are well within the realm of routine experimentation. Applicants submit that the techniques of combinatorial mutagenesis and high through-put screening are well-known in the art at the time of filing (for review, see Gallop et al., *J. Med. Chem.* 1994, *37,* 1233-1251), making the identification of active polypeptides having up to six mutated amino acids routine, if not trivial. In addition, there are a number of art-recognized methods for screening random mutations affecting binding affinity between proteins. For example, WO 96/32503 A1 (published on October 17, 1996) teaches a reverse two-hybrid system for efficient identification of mutations that can result in either loss or acquired protein-protein interactions. Thus, it is not only possible but also routine to identify mutant IL-11R that can interrupt the ternary complex formation. Contrary to the Examiner's suggestion, such screening methods inherently do not depend on information gathered from those already known mutants as disclosed in the instant application. In addition, even if most of these random mutations do not yield polypeptides with desired characteristics as the Office Action suggests, the very purpose of the assays is to distinguish the active mutants from the

inactive ones. Accordingly, only routine experimentation would be required to synthesize and identify active mutants.

Finally, there is a minor but important distinction between the mutant IL-11R screen procedure mentioned above and the one suggested by the Examiner ("to test all possible mutations ... in the region of IL-11R sequence that can bind to IL-11."). Applicants submit that the method taught by the specification does not *require* testing of *all* possible mutations in the IL-11/IL-11R binding region. Rather, a screen of randomly generated mutants within the IL-11/IL-11R binding region is desired, whether or not these randomly generated mutants indeed encompass *all* possible mutations within the IL-11R binding domain. The fact remains that any randomly generated mutants would fall somewhere within the scope of the pending claims, and that any narrowing of scope would result in some easily accessed random mutations falling outside the scope of the narrowed claims, a result not mandated by, and in fact contrary to, the enablement requirement.

The Office Action also asserts that the "recitation of 'an IL-11 binding peptide' in claim 11 and 12 is extremely broad and encompasses several classes of molecules that fit the description of a 'IL-11 binding peptide.'" Specifically, the Office Action suggests that "the specification is enabled for a binding peptide with a selected region representing its receptor binding region of the sequence 'RRLRASW'. However, the disclosure is non-enabling for other binding peptides of IL-11 that have not been envisioned" and thus it requires undue experimentation to identify those not yet envisioned binding IL-11 peptides. Applicants respectfully disagree.

First of all, the specification has taught at least one other class of IL-11 binding peptide, including SEQ ID No. 6 (page 9, line 31) and SEQ ID No. 8 (page 10, line 19), that is non-overlapping with the "RRLRASW"-containing SEQ ID No. 1.

Secondly, the specification has set forth the identity of those IL-11 binding peptides, including variations of SEQ ID Nos. 1, 5-8 and 10, as well as other peptides substantially different from those above mentioned SEQ ID Nos. (page 9-11), and how to identify other such peptides using art-recognized or disclosed methods such as bone nodule formation assay or TRAP assay. Thus the meaning of "IL-11 binding peptide" as used herein is clear and fully enabled. None of the claimed peptides are "not envisioned," as suggested by the Examiner. However, if the Examiner means that there might be other not yet envisioned "IL-11 binding peptides" at the time of filing of

the instant application, which would nonetheless literally fall within the scope of the term "IL-11 binding peptide," Applicants submit that the full scope of the claim is still enabled in view of *In re Hogan*, 559 F.2d 595 (CCPA 1977). In that case, Appellants claimed "A normally solid homopolymer" when, at the time of filing, only the crystalline form of the homopolymer was known to the art. However, later development in the art created an amorphous form of the homopolymer which is not known at the time of filing but nonetheless literally fall within the scope of the broader term "solid homopolymer." In reversing the rejection of the Board, the Court (CCPA) affirmed that the original broad claim scope of "solid homopolymer" is enabled and encompasses the amorphous homopolymer resulting from later development of the art.

Applicants also wish to point out that the non-effective peptide 2 in Example 5 is not an IL-11 binding peptide and therefore is non-effective in inhibiting ternary complex formation, as shown in Example 5. This is an example of how one can differentiate between candidate IL-11 binding peptides using routine experimentation according to the teaching of the specification.

The Office Action also asserts that the "recitation of 'a small molecule' in claim 14 is extremely broad in that the nature of such a small molecule is left open for determination by the skilled artisan." The Office Action also inquires about the nature of these small molecules and the nature of their action (such as via binding to components of the ternary complex or via changing the environment for ternary complex formation, etc.). The Examiner also suggests that undue experimentation is required to identify these small molecules.

Applicants submit that the specification has defined "small molecule" as "a compound having a molecular weight of no more than 30 kd." (page 12, lines 10-11). Thus, as to their chemical nature, a skilled artisan will readily appreciate that "small molecule" can encompass a diverse array of molecules such as small chemical (natural or synthetic) compound, small peptides, small polynucleotides, or lipids, etc., which have a molecular weight of less than 30 kd.

As to the mode of action of such small molecules, Applicants submit that Applicants are not required to state *why* the invention works. As stated in MPEP 2138.05, *Parker v. Frilette*, 462 F.2d 544, 547, 174 USPQ 321, 324 (CCPA) ("[an] inventor need not understand precisely why his invention works in order to achieve an actual reduction to practice"). Therefore, Applicants submit

that this line of argument is irrelevant to the enablement of the presently claimed invention as it pertains to small molecules.

As to the identification of those small molecules, the specification has set forth the procedure to follow by using art-recognized or disclosed methods such as bone nodule formation assay or TRAP assay (page 12, lines 10-28). In addition, Applicants submit that high efficiency synthesis of small chemical compound libraries or peptide libraries (see U.S. Pat. No. 5,532,167, issued on July 2, 1996) useful for these assays were well known in the art at the time of filing, and thus it would have been merely routine experimentation to screen those libraries to identify small molecules capable of inhibiting the formation of ternary complex using the TRAP assay or bone nodule formation assay.

The Office Action also asserts that the "recitation of 'IL-11 antagonist' in claim 15 is overly broad in encompassing IL-11 mutants, or IL-11 antibodies, or short binding peptides (to) IL-11, or IL-11R binding peptides." Applicants submit that the specification has set forth the definition of "IL-11 antagonist" in page 12, lines 11-14, as "a compound which inhibit or prevent the productive interaction between IL-11 and IL-11R and which are less effective than IL-11 at promoting the productive interaction of IL-11R and gp130." Thus, "IL-11 antagonist" at least also includes a mutant IL-11R that is mutated in its gp130-binding region, as disclosed in the specification, particularly Examples 6 and 7 and the claims.

Secondly, as mentioned above, it merely would have required routine experimentation for a skilled artisan to determine if any molecule falling into any of the classes cited by the Office Action (or even those not so recited) is in fact an IL-11 antagonist by using an art-recognized or disclosed TRAP assay or bone nodule formation assay. Therefore, no undue experimentation would have been required to practice the claimed invention, and the specification is enabling for claim 15.

The Office Action also asserts that the "recitation of 'IL-11R binding peptide' in claim 16 is extremely broad without describing specifically whether 'the binding peptide' is a portion of the IL-11R antibody, or a portion of the IL-11." The Office Action also suggests that, if the peptide is an IL-11R antibody, and in the absence of guidance as to the specificity of the antibodies with respect to its antigen binding site, it would not be able to efficiently block the formation of a

ternary complex formation. Applicants respectfully disagree. While Applicants concur that each antibody may be specific for a specific epitope of a given antigen, it is neither possible nor necessary for Applicants to describe the specificity of each and every antibody against IL-11R to practice the instant invention. To practice the instant invention, a skilled artisan need only follow the guidance provided in the specification, namely to use the art-recognized or disclosed TRAP and/or bone nodule formation assay, to determine if any given antibody is effective in blocking the formation of the ternary complex in vivo.

In summary, based on facts and arguments presented above, Applicants submit that the specification is fully enabling for the invention as claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

Claim rejections under 35 USC §112, second paragraph

Claims 1-18, 40 and 41 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Particularly, the Examiner suggests that claims 1, 40 and 41 recite use of acronyms which are not spelled out when first used. Accordingly, Applicants have adopted the Examiner's suggestion and amended claim 1 to clarify this issue. Applicants submit that there is no narrowing of scope due to this amendment.

The Office Action also states that claims 40 and 41 reciting "a composition of matter" "comprising an antibody..." are improper since a composition of matter consists of more than one ingredient, and thus includes more than just one antibody. For clarification purpose only, Applicants have amended these claims as shown to eliminate "of matter." However, Applicants submit that there is no scope change in the amended claims since the transitional phrase "comprising" is open-ended and thus necessarily permits the inclusion of more than just one antibody. This is true even for the term "a composition comprising an antibody" suggested by the Examiner. In fact, for effective use of the antibody, ingredients such as proper salt solutions, other excipients necessary for *in vivo* use of the antibody, and additional components useful for

enhancing the effects / stability of the antibody may be included in the composition, as would be understood by one of skill in the art.

Applicants have amended claim 13 to replace the direct recitation of the triplet code amino acid sequence with its corresponding SEQ ID No.

The Office Action asserts that claim 1 is indefinite for being "without positive recitation of steps necessary to inhibit the complex formation." Applicants respectfully disagree. Claim 1 is a broad generic claim in which the only method step is "inhibiting the formation of ternary complex..." Thus, claim 1 has one positive recitation of a step. The claim set forth the inventive concept of disrupting the formation of a ternary complex between IL-11/IL-11R/gp130 for the treatment of bone density loss. Applicants submit that the language itself makes clear the boundaries of the subject matter for which protection is sought, which is all that is required to satisfy the 2nd paragraph of 35 U.S.C. 112. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action also states that the meaning of "interaction" other than "binding," as used in claim 40 and 41 is unclear. Applicants submit that a skilled artisan would appreciate that "interaction" as used herein is a common biological term for "binding." It is used in most, if not all, cases interchangeably with "binding," particularly in the context of referring to "protein-protein interaction." Therefore, the meaning of "interaction" is not unclear. Nevertheless, for clarity purpose, Applicants have amended the claims to comply with the Examiner's requirement. Applicants submit that there is no narrowing of scope in any respect due to this amendment, and reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action states that claim 4 is "indefinite in reciting 'small molecule' because it is not clear as to what is the definition of a small molecule in selecting a compound for the claimed invention." Applicants assume that the Examiner meant to refer to claim 14 rather than claim 4, which does not refer to "small molecule." In page 12, lines 10-11, the specification specifically set forth that "the term 'small molecule' refers to a compound having a molecular weight of no more than 30 kd." Nevertheless, for clarification purpose, Applicants have included this definition expressly in claim 14 to obviate this rejection. Because this term was so defined in the specification, Applicants submit that there is no narrowing of scope due to this amendment.

The Office Action further states that claim 15 is vague in reciting "IL-11 antagonist" since this might include IL-11R itself. Applicants submit that the specification has set forth the definition of "IL-11 antagonist" in page 12, lines 11-14, as "a compound which inhibit or prevent the productive interaction between IL-11 and IL-11R and which are less effective than IL-11 at promoting the productive interaction of IL-11R and gp130." Wild-type IL-11R itself clearly does not fall into that definition, since IL-11R would not "inhibit or prevent the productive interaction" between IL-11 and itself. In addition, IL-11R would not be "less effective than IL-11 at promoting the productive interaction of IL-11R and gp130." Since Applicants are allowed to be their own lexicographer as long as the meaning of a word is not repugnant to its usual meaning (MPEP 2173.05(a)), and a skilled artisan would agree that the term "IL-11 antagonist" does not have a usual meaning of "IL-11R," Applicants submit that the term is clear when read in light of the specification. Thus, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the amendments and arguments presented above, Applicants respectfully request that the Examiner reconsider and withdraw all rejections under 35 U.S.C. 112, second paragraph.

Claim rejections under 35 USC §102(b)

Claims 1-18, 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 9619574.

Particularly, the Office Action states that WO 9619574 teaches "methods of inhibiting binding of IL-11 to the human IL-11R in a mammalian subject" with a "human IL-11R protein, an inhibitor, or an antibody to a human IL-11R protein," and "methods of treating or preventing loss of bone mass in a mammalian subject using these compositions." Applicants respectfully disagree for the reasons that follow.

Claim 1 of the instant application is directed to a method / process of treating a condition *in vivo* by "inhibiting the formation of a tertiary complex of IL-11, IL-11R, and gp130." Applicants submit that WO 9619574 is non-enabling in terms of "treating or alleviating the symptoms of a pathological condition in which bone density is decreased in a mammalian patient (*in vivo*) suffering from such a condition."

It is well known in the art that, in certain instances, *in vitro* data may not reliably predict *in vivo* effects, as has been the case with IL-11. The family of cytokines to which IL-11 belongs is marked by redundancy and overlapping pleiotropic effects. IL-11 was first characterized as a hematopoietic cytokine with thrombopoietic activity in 1990. Although studied extensively in the hematopoietic system, its physiological roles in both the hematopoietic system and non-hematopoietic system (such as bone remodeling) are unclear. While it may be easy to imagine that inhibiting the tertiary complex formation *in vivo* might be effective in preventing osteoclastogenesis based on some *in vitro* data, previous studies suggest that cytokine redundancy *in vivo* may render IL-11 unnecessary for one of its supposedly important functions *in vitro* - controlling the proliferation of hematopoietic progenitor cells. Particularly, Nandurkar et al. (Blood 90: 2148-2159, 1997, provided as **Exhibit B**), published after WO 9619574, demonstrated that mice lacking IL-11R showed wild-type level of adult hematopoiesis, indicating that preventing the formation of IL-11/IL-11R/gp130 tertiary complex *in vivo*, as accomplished by Nandurkar et al. by "knocking out" the IL-11R, may not achieve the same effect seen *in vitro*. Since WO 9619574 just provides a conclusory prediction without any experimental support (neither *in vivo* nor *in vitro*), in view of the teachings of Nandurkar et al., a skilled artisan, absent the teachings of the present specification, would have relied on Nandurkar et al. and concluded that inhibition of IL-11 activity *in vivo* would have no measurable effect on osteoblast or osteoclast function as other cytokines may compensate for the inhibition of IL-11 activity. Indeed, the Romas reference notes that IL-6 and IL-1 may be involved in osteoclast formation. Therefore, Applicants submit that WO 9619574 is non-enabling for *in vivo* treatment of bone density loss and a skilled artisan would not, *a priori*, have a reasonable expectation that antagonism of IL-11 would produce any effect *in vivo* in light of the teachings of Nandurkar et al.

Rather, it is the *in vivo* data first presented by Applicants that finally provides the proof that antagonism of IL-11 activity *in vivo* can produce a change in the rate of bone resorption and bone formation, thus enabling the claimed *in vivo* treatment method. Accordingly, Applicants submit that since WO 9619574 is non-enabling for the claimed *in vivo* treatment methods, there is no evidence of prior public possession before the instant invention by the Applicants. Therefore, WO 9619574 does not anticipate the claimed *in vivo* treatment methods, and reconsideration and withdrawal of rejection under 35 U.S.C. 102(b) is respectfully requested.